REMARKS

I. Status of the Claims and support for the Amendments

Claim 1 is currently amended.

Claim 23 has been cancelled. Withdrawn claims 7-9, 11-13, and 27-34 are cancelled in this action.

Claims 37-42 have been added. Support for the new claims can be found in pages 11-13 and in the Sequence Disclosure.

Claims 1, 24-26, and 35-42 are currently under examination.

II. Amendments to the Specification

The amendments to the specification are in response to Examiner's objection to the form of the reference to trademarks used in the specification.

Support for the new claims 37-42 can be found on pages 11 through 13 of the specification. Specifically, new claims 37 and 38 are directed to peptides that have repeat sequences of XG that meet the formula $(XG)_{2\text{-}9}$ (See Seq ID Nos:1-15) and $(XG)_{4\text{-}9}$ (See Seq ID Nos:1, 4, 5 & 7), respectively. New claim 39 is directed to peptides with $(XG)_2$ sequences with one or more XG sequences separated by one or more intervening amino acids. *See* SEQ ID NOs:2, 3, 6 and 8-15. New claims 40-42 are supported by SEQ ID NOs:1-15.

III. Claim Rejections

A. 35 USC § 112 ¶ 1—New Matter Rejections

The Examiner rejected Claims 1, 23-26, and 35-36 under 35 USC § 112 ¶ 1 as allegedly being new matter for its use of the terms "asymmetrical dimethyl arginine" and "symmetrical dimethyl arginine". The Applicant respectfully disagrees.

Throughout the specification and the claims, the term "methylated arginine" is used in a broad sense to refer to both mono- and dimethylated arginine. In view of the specification and the claims, Applicant asserts that the meanings of "symmetrical" and "asymmetrical" are readily apparent to one of ordinary skill in the art. At page 8, lines 27-30 the specification recites:

> [a]ccording to its main embodiment the present invention relates to peptides that contain arginine residues that are immediately followed by a glycine residue, and wherein at least one arginine residue is methylated or dimethylated at one terminal amino group of the guanidino-group of the arginine residue.

Additionally, referring to the methylated peptide, page 12, lines 12-13 of the specification recite "wherein at least one and preferably each arginine is methylated, preferably dimethylated and even more *preferably dimethylated in an asymmetric way.*" (emphasis added). Claim 1 has been amended to recite "wherein X stands for a N^G-mono- or N^G-N^G-dimethylated arginine, or N^G-$N^{G'}$-dimethylated arginine".

One of ordinary skill in the art knows that the term "dimethyl-arginine" encompasses asymmetrically dimethylated and symmetrically dimethylated arginine. Applicant includes with this response printouts from the SigmaAldrich Online Catalog showing the structure of asymmetric dimethtylarginine (*i.e.*, N^GN^G-Dimethylarginine, or asym-dimethylarginine, or ADMA) and the corresponding common nomenclature for asymmetric dimethtylarginine (i.e., $N^GN^{G'}$-Dimethylarginine, or SDMA). Applicant has also included an abstract to the reference: Nijveldt et al., *Handling of asymmetrical dimethylarginine and symmetrical dimethylarginine by the rat kidney under basal conditions and during endotoxaemia*; Nephrol Dial Transplant. 2003 Dec; 18(12):2542-50. Nijveldt et al. uses the common abbreviations ADMA and SDMA interchangeably for asymmetrical dimethylarginine and symmetrical dimethylarginine, respectively. As stated above, SDMA refers to $N^GN^{G'}$-Dimethylarginine.

To avoid ambiguity in the claims, the Applicant has amended claim 1 to reflect only the commonly-used nomenclature of N^G-N^G-dimethylated arginine, or N^G-$N^{G'}$-dimethylated arginine to indentify asymmetrically dimethylated and symmetrically dimethylated arginine, respectively. This type of nomenclature is used in the current Specification (*See, e.g.*, Specification p. 7). In view of the foregoing explanation, Applicant believes that the rejection of claim 1 and its dependent claims, 24-26, and 35-36 have been overcome.

B. 35 USC § 112 ¶ 1—Written Description Rejections

Examiner rejects claims 1, 24-26 and 35-36 for allegedly failing to comply with the written description requirement. Specifically, the Examiner stated: "Applicant has not described a function that is shared by the claimed branched peptide that would adequately describe the genus." (Office Action, p. 5). In response, the Applicant has amended independent claim 1 to limit the claims to a peptide that: "is able to react with antibodies and with said methylation being crucial for the reaction between said peptide and said antibodies and wherein said antibodies are present in sera from patients with systemic lupus erythematosus (SLE)." Page 9 ll. 7-23 and pages 12-13 of the current Specification supports the amendment to claim 1. Within said cited specification pages, Applicant discloses several representative peptides that comprise constituents of the claimed genus, particularly, antigenic peptides of SmD1 (SEQ ID NOs:16-18), SmD3 (SEQ ID NO:19), Sm69 (SEQ ID NOs:20-27), and Epstein Barr Virus nuclear antigen 1 (SEQ ID NOs:28-30), and fragments of each. SEQ ID NOs:16-30 are the unmethylated forms of the corresponding Xaa-substituted sequences disclosed as SEQ ID NOs:1-15. SmD1, SmD3, and Sm69 react with antibodies in sera from SLE patients. The peptide sequences that comprise the representative species all contain the XG motif. Applicant also directs the Examiner to Example 6 (Specification, page 36) and figures cited therein, which

show that methylation and dimethylation of arginine in the claimed XG motif is required for recognition by antibodies in sera from patients with SLE.

The Examiner has also rejected claim 23 for allegedly lacking an adequate written description. Applicant has cancelled claim 23, so the rejection is now moot. As the matter of claim 23 has been substantially incorporated into independent claim 1, the Applicant will address the Examiner's remarks made thereto. Specifically, the Examiner stated:

> To fulfill the written description requirements...the specification must describe ... a representative member of the claimed genus, *which shares a particularly defining feature common to at least a substantial number of the members of the claimed genus*, which would enable the skilled artisan to immediately recognize and distinguish its members from others, so as to reasonably convey to the skilled artisan that Applicant has possession of the claimed invention.

The present invention is the discovery that antibodies responsible for deleterious effects in the autoimmune disease SLE specifically require <u>methylation</u> of an XG motif present within the claimed antigenic peptides. To quote the specification:

> [T]the present invention relates to peptides that contain arginine residues that are immediately followed by a glycine residue, and wherein at least one arginine residue is methylated or dimethylated at one terminal amino group of the guanidino-group of the arginine residue, and wherein this methylation is a prerequisite for the peptide to be recognized by antibodies that characterize certain diseases. Antibodies that are specifically reacting with this type of peptides can be found in sera from patients with systemic lupus erythematosus or related autoimmune diseases . . .

Specification, p. 8 ll. 27-31; p. 9 ll. 1-3.

The requirement for methylation of at least one XG motif present in the claimed peptides distinguishes the present invention from the prior art. In response to Examiner's rejection, this limitation is now incorporated into amended claim 1 with the added language: "<u>with said methylation being crucial for the reaction between said peptide and said antibodies</u>". The applicant discloses that the claimed peptides should have no less than one methylated or

(preferably) an asymmetric dimethylated arginine residue, but may also contain repeats of such motifs according to the formula $(XG)_{2-9}$. (Specification, p. 12).

The Examiner states that Applicant must disclose relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. The Examiner further cites Skolnick et al. (*Trends in Biotechnology* 18: 34-39, 2000) in support of the assertion that this application concerns an "unpredictable art". Based on that conclusion, the Examiner quotes *The Guidelines for Examination of Patent Applications Under 35 USC § 112, paragraph 1, "Written Description" Requirement*, 66 FR 1099, 1106 (2000) for the applicable standard: "For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only **one** species within a genus."

The methylated XG motif within the claimed SLE antigenic peptides is the distinguishing identifying characteristics of the claimed invention. Further, even if this application concerns an unpredictable art, the specification discloses not one, but several representative examples of peptides that comprise members of the claimed genus designated SEQ ID NO:16-30 on pages 12-13 of the current specification. Again, SEQ ID NO 16-30 are the unmethylated forms of the corresponding Xaa-substituted sequences disclosed and claimed as SEQ ID NOs:1-15. Each of the disclosed sequences shares the common distinguishing identifying characteristic of having at least one mono- or dimethylated XG motif. Example 6 and the figures cited therein further shows that mono- or dimethylated XG motif distinguishes the present invention from peptides known in the prior art. In other words, the structure—peptides of various size with mono or dimethylated XG dimers—dictates the function, *i.e.*, recognition by SLE antibodies.

In view of the amendments to claim 1, the canceling of claim 23, and the foregoing remarks, applicant believes that the Examiner's written description rejections to claims 1, 23-26, and 35-36 have been overcome.

C. 35 USC § 102(b)—Prior Art Rejections

The Examiner rejected claims 1, 24, 26, and 35-36 as allegedly anticipated by both Rajpurohit et al. (Biochim Biophys Acta. 1992 July 31; 1122(2) pp. 183-88) and Rawal et al. (Biochemica et Biophysica Acta Vol. 1248, 1995, pp. 11-18). As cited by MPEP § 2131, under § 102(b), "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of Cal.*, 814 F.2d 628, 631 (Fed. Cir. 1987). Further, "[t]he identical invention must be shown in as complete detail as is contained in ... the claim." MPEP § 2131 (quoting *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989).

The Examiner's citation to Rajpurohit et al. as 102(b) prior art does not meet the above-quoted standards. While the Rajpurohit et al. publication discloses peptides containing N^G-monomethylated and N^GN^G- dimethylated arginine residues, the authors do not disclose an XG motif (i.e., no requirement for a neighboring Glycine was ever mentioned), nor is the element inherently described. *See Schering Corp. v. Geneva Pharma.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003) ("A prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating reference.") That a methylated XG peptide *might* have resulted from the hydrolysis described in the Rajpurohit et al. article does not mean that such a peptide was necessarily present as required for anticipation. Further, as currently amended claim 1 requires that the claimed methylated peptides are able to react with antibodies in sera from SLE patients. The Rajpurohit et al.

publication does not mention reactivity of the peptides in sera of SLE patients. Accordingly, the Applicant believes that the Rajpurohit et al. is not an anticipatory reference under § 102(b).

Examiner's 102(b) rejection based on Rawal et al. (1995) was because the authors "disclose branched peptides of less than 50 amino acids comprising at least one XG dimer." Applicant respectfully disagrees. Applicant understands that Rawal et al. article discloses only a single cyclized peptide with the sequence CGKGRGLC (*See* Rawal et al., abstract and p. 13). Accordingly, Rawal et al. do not anticipate branched amino acids of claim one. New claim 42 has been added as a result. The single cyclized peptide in Rawal et al. is eight amino acids in length. Accordingly, new claim 40 (drawn to peptides longer than eight amino acids) is not anticipated by Rawal et al. for either branched or cyclized peptides. In addition, Applicant has also added new claim 41 drawn to peptides longer than ten amino acids. New claim 41 supported by the SEQ ID NO:2. New claims 37 and 38 are directed to peptides that have repeat sequences of XG that meet the formula $(XG)_{2\text{-}9}$ (*See* Seq ID Nos:1-15) and $(XG)_{4\text{-}9}$ (*See* Seq ID Nos:1, 4, 5 & 7), respectively. New claim 39 is directed to peptides with $(XG)_2$ sequences with one or more XG sequences separated by intervening peptides. *See* SEQ ID NOs:2, 3, 6 and 8-15. Rawal et al. do not disclose cyclized or branched peptides meeting these limitations. Further support for the foregoing amendments to the claims is found in pages 11-13 of the Specification and in the Sequence Disclosure.

Most importantly, Rawal et al. describes the enzymatic methylation of polypeptides on arginine residues, and observed that the methylated arginines were present in RG-rich motifs. It is known that methylation is one of the many post-translational modifications catalyzed by highly-specific methyltransferases. *See* Rawal et al. ("Many highly specialized proteins have been found to contain methylated arginine derivatives; MBP, histones, heatshock proteins,

hnRNP proteins, nuleolin, fibrillalin, HMG protein, and tooth matrix protein."). Rawal et al. only investigated the structural features that are essential for serving as a substrate for Protein methylase I. Rawal et al. concluded that the function of Protein A1 methylation was unknown and speculated that methylation "*may* modulate the nucleic acid binding properties" of the enzyme. Rawal et al. at 18 (emphasis added). Rawal et al. did not discuss antibody binding affinities or link RG methylation to autoimmune or other diseases, specifically SLE. Accordingly, Applicant believes that Rawal et al. does not anticipate the claims as they are now presented.

VI. Conclusion

In view of the foregoing Amendments and Remarks, Applicant believes that all rejections of and objections to the instant application have been overcome. Consequently, Applicant respectfully requests favorable reconsideration of the application and timely issuance of a Notice of Allowance therefor.

Respectfully submitted,

Patricia A. Kammerer
Reg. No. 27,775
Attorney for Assignee
INNOGENETICS N.V.

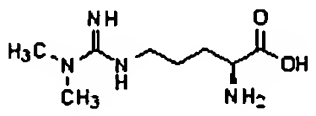
CUSTOMER NO. 23369
HOWREY LLP
1111 Louisiana, 25th Floor
Houston, TX 77002-5242
(713) 787-1438

Date: May 12, 2006

www.sigma-aldrich.com

D4268 N^G,N^G-Dimethylarginine dihydrochloride

Sigma



Synonym	*asym*-Dimethylarginine
	ADMA
Molecular Formula	$C_8H_{18}N_4O_2 \cdot 2HCl$
Molecular Weight	275.18
CAS Number	220805-22-1
MDL number	MFCD00038406

Expand/Collapse All

Price and Availability

Click For Pricing and Availability

Descriptions

Biochem/physiol Actions Reversible inhibitor of nitric oxide synthetase *in vivo* and *in vitro*.

References

Reference Vallance, P., et al. *Lancet* **339**, 572, (1992) abstract

Safety

WGK Germany 3

Related Categories

... Nitric Oxide Metabolism > **Nitric Oxide Synthase Regulators**

D0390 $N^G,N^{G'}$-Dimethyl-L-arginine di(p-hydroxyazobenzene-p'-sulfonate) salt

Sigma **>99% (TLC)**

Synonym	SDMA
Molecular Formula	$C_8H_{18}N_4O_2 \cdot 2C_{12}H_{10}N_2O_4S$
Molecular Weight	758.82
CAS Number	102783-24-4
MDL number	MFCD00070085

Expand/Collapse All

Price and Availability

Click For Pricing and Availability

References

Reference Vallance, P., e.t al. *Lancet* **339**, 572-575 , (1992)

Safety

WGK Germany 3

Related Categories

... Enzy: Hydrolase > EC 3

Note: Performing your original search, ***symmetrical dimethylarginine SDMA***, in PubMed will retrieve *21* citations.

1: Nephrol Dial Transplant. 2003 Dec;18(12):2542-50.

Handling of asymmetrical dimethylarginine and symmetrical dimethylarginine by the rat kidney under basal conditions and during endotoxaemia.

Nijveldt RJ, Teerlink T, van Guldener C, Prins HA, van Lambalgen AA, Stehouwer CD, Rauwerda JA, van Leeuwen PA.

Department of Surgery, VU University Medical Center, 1007 MB Amsterdam, The Netherlands.

BACKGROUND: Asymmetrical dimethylarginine (ADMA) is capable of inhibiting nitric oxide synthase enzymes, whereas symmetrical dimethylarginine (SDMA) competes with arginine transport. The potential role of inflammation in the metabolism of ADMA has been elucidated in an in vitro model using tumour necrosis factor-alpha, resulting in a decreased activity of the ADMA-degrading enzyme dimethylarginine dimethylaminohydrolase (DDAH). The kidney probably plays a crucial role in the metabolism of ADMA by both urinary excretion and degradation by DDAH. We aimed to further elucidate the role of the kidney in a rat model under basal conditions and during endotoxaemia. METHODS: Twenty-five male Wistar rats weighing 275-300 g were used for this study. The combination of arteriovenous concentration differences and kidney blood flow allowed calculation of net organ fluxes. Blood flow was measured using radiolabelled microspheres according to the reference sample method. Concentrations of ADMA, SDMA and arginine were measured by high-performance liquid chromatography. RESULTS: The kidney showed net uptake of both ADMA and SDMA and fractional extraction rates were 35% and 31%, respectively. Endotoxaemia resulted in a lower systemic ADMA concentration ($P = 0.01$), which was not explained by an increased net renal uptake. Systemic SDMA concentrations increased during endotoxaemia ($P = 0.007$), which was accompanied by increased creatinine concentrations. CONCLUSIONS: The rat kidney plays a crucial role in the regulation of concentrations of dimethylarginines, as both ADMA and SDMA were eliminated from the systemic circulation in substantial amounts. Furthermore, evidence for the role of endotoxaemia in the metabolism of dimethylarginines was obtained as plasma levels of ADMA were significantly lower in endotoxaemic rats.

PMID: 14605276 [PubMed - indexed for MEDLINE]